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Attorney's Docket No.: 14875-137US1 / C1-A0210Y1P-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: Tatsuhiko Kodama et al.	Art Unit	: 1644
Serial No.	: 10/516,603	Examiner	: Unknown
Filed	: June 8, 2005		
Title	: METHODS FOR PRODUCING ANTIBODIES		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

REQUEST FOR CORRECTED OFFICIAL FILING RECEIPT

Please correct the title shown on the Filing Receipt for the above-referenced application to read: "**METHODS FOR PRODUCING ANTIBODIES**". This is the title as amended in the Preliminary Amendment (copy enclosed) filed with the application on June 8, 2005. A copy of the original Filing Receipt showing the desired changes in red ink is attached for your convenience. Please supply a corrected Filing Receipt to the undersigned.

No fee is believed to be due. If, however, there are any charges or credits, apply them to Deposit Account No. 06-1050.

Respectfully submitted,

Date: Aug. 15, 2005

Janis K. Fraser, Ph.D., J.D.
Reg. No. 34,819

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

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I hereby certify under 37 CFR §1.8(a) that this correspondence is being deposited with the United States Postal Service as first class mail with sufficient postage on the date indicated below and is addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450.

August 16, 2005
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10/516,603	06/08/2005	1644	1256	14875-137US1	9	20	5

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CONFIRMATION NO. 5647

26161
FISH & RICHARDSON PC
225 FRANKLIN ST
BOSTON, MA 02110

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Action Code: COR FLG RCPT
Base Date: 6-17-05
Due Date: 7-17-05
Deadline: 7-17-05
Initial: VMA

FILING RECEIPT

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Date Mailed: 06/17/2005

Receipt is acknowledged of this regular Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. **If an error is noted on this Filing Receipt, please mail to the Commissioner for Patents P.O. Box 1450 Alexandria Va 22313-1450. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).**

Applicant(s)

Tatsuhiko Kodama, Tokyo, JAPAN;
Kou-Ichi Jishage, Shizuoka, JAPAN;
Nobuo Kamada, Zhizuoka, JAPAN;
Yoshiki Yamada, Shizuoka, JAPAN;

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JUN 23 2005
ANIS K. FRASER

Power of Attorney: The patent practitioners associated with Customer Number **26161**.

Domestic Priority data as claimed by applicant

This application is a 371 of PCT/JP03/07071 06/04/2003

Foreign Applications

JAPAN 2002-164834 06/05/2002
JAPAN 2002-180351 06/20/2002

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Title

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~~Method of constructing antibody~~ methods for Producing Antibodies

Preliminary Class

530

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Title 35, United States Code, Section 184
Title 37, Code of Federal Regulations, 5.11 & 5.15

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AUG 18 2005
PATENT & TRADEMARK OFFICE

Attorney's Docket No.: 14875-137US1 / C1-A0210Y1P-US

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Kodama et al.
Serial No. : Unassigned
Filed : Herewith
Title : METHODS FOR PRODUCING ANTIBODIES

Art Unit : Unknown
Examiner : Unknown

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Alexandria, VA 22313-1450

PRELIMINARY AMENDMENT

Prior to examination, please amend the application as indicated on the following pages (a total of 11, including this page).

Amendments to the Specification appear at pages 2-6.

Amendments to the Claims appear at pages 7-9.

Amendment to the Drawings appear at page 10.

Remarks appear at page 11.

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Amendments to the Specification:

Please replace the original paper copy of the Sequence Listing with the substitute paper copy of the Sequence Listing filed herewith.

At page 1, line 1, please delete subheading:

~~DESCRIPTION~~

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Please amend the title to read as:

METHODS FOR PRODUCING ANTIBODIES

Insert the following paragraph on page 1, line 3, after the title:

Claim of Priority

This application is the National Stage of International Application No. PCT/JP03/07071, filed June 4, 2003, which claims the benefit of Japanese Patent Application Serial Nos. 2002-164834, filed on June 5, 2002, and 2002-180351, filed on June 20, 2002, the entire contents of which are hereby incorporated by reference.

Please replace the paragraph beginning at page 7, line 25, with the following amended paragraph:

Of these methods, transgenic non-human animals which preserve a gene encoding an immunotolerance antigen in an expressible state are preferred as the non-human animals comprising immunotolerance of the present invention. The transgenic animals comprise in their body an immunotolerance antigen that was originally an exogenous protein prior to the maturation of immune functions. Therefore, it is highly possible that the immune functions of the transgenic animals recognize the immunotolerance antigen as being completely endogenous. Thus, the use of such transgenic non-human animals is advantageous in inducing immunotolerance in the present invention. The transgenic animals, into which immunotolerance

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antigens are introduced, produce few antibodies to immunotolerance antigens, as shown in Example[[s]] 8.

Please replace the paragraph beginning at page 17, line 6, with the following amended paragraph:

More specifically, transgenic mice can be prepared, for example, by the method in Example[[s]] 2.

Please replace the paragraph beginning at page 24, line 7, with the following amended paragraph:

Fig. 3 shows the structure of the pCAG-gp64 vector constructed in Example[[s]] 1.

Please replace the paragraph beginning at page 25, line 6 with the following amended paragraph:

The PCR reaction solution composition was 5 μl of x10 ExTaq buffer, 4 μl of dNTP supplied with ExTaq, 1 μl of 10 μmol/l 64F1 primer, 1μl of 10 μmol/l 64R1 primer, 1μl of 500 pg/μl pBac-N-blue, 0.5 μl of 5 units/μl ExTaq, and 37.5 μl of deionized water (DIW). PCR was carried out for:
5 minutes at 94°C;
25 cycles of "15 seconds at 94°C, 30 seconds at 57°C, and 30 seconds at 72°C";
7 minutes at 72°C; and
4°C forever.

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Please replace the paragraph beginning at page 25, line 15, with the following amended paragraph:

The amplified band was subcloned into pGEM-Teasy, and then transformed *E. coli* DH5α cells. After performing colony PCR using T7 and SP6 primers, the nucleotide sequence of clones confirmed to comprise the insert was analyzed with the ~~ABI Prism377 DNA sequencer~~

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~~and the BigDye Cycle Sequence kit~~ ABI Prism® 377 DNA sequencer (Applied Biosystems) and the BigDye® Terminator Cycle Sequencing kit (Applied Biosystems), in combination with the T7 primer or the SP6 primer. As a result, clones comprising the subject gene were confirmed. A fragment comprising the gp64 gene and confirmed to comprise no mutations in its nucleotide sequence was isolated from the clones by EcoRI digestion, and then inserted into an EcoRI-digested pCAGGS1. The resulting vector was used to transform *E. coli* DH5α cells. Cells comprising the clone as designed were incubated in 250 ml of LB medium at 37°C overnight, and purified by using the Endofree MAXI kit (QIAGEN) to obtain 581.6 μg of plasmid.

Please replace the paragraph beginning at page 25, line 36, with the following amended paragraph:

The mouse pronuclear eggs to be injected with the DNA fragment were collected as follows: Specifically, BALB/c series female mice (Nippon CLEA) were induced to superovulate by intraperitoneal administration of 5 international units (i.u) of pregnant mare serum gonadotrophin (PMSG), followed by intraperitoneal administration of 5 i.u of human chorionic gonadotrophin (hCG) 48 hours later. These female mice were mated with male mice of the same lineage. The morning after mating, the oviducts of female mice that were confirmed to have a vaginal plug were perfused to recover pronuclear eggs.

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Please replace the paragraph beginning at page 26, line 8, with the following amended paragraph:

The DNA fragments were injected into the pronuclear eggs with a micromanipulator (Experimental Medicine (Jikken Igaku) suppl., [[(]] The latest technologies in gene targeting (gene targeting no saishin gijyutu) (Yodosha), 190-207, 2000). The DNA fragments were injected into 373 embryos of BALB/c mice. On the next day, 216 embryos that had developed to the two-cell stage were transplanted into the oviducts of recipient female mice, which were in the first day of pseudopregnancy, at a density of around ten embryos per oviduct (i.e. around 20 embryos per mouse).

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Please replace the Table 2 on page 27 with the following amended Table 2:

Table 2

Line No.	Date of birth	Sex	Copy Number of the introduced gene	Offspring obtained (date of birth, total offspring, and Tgm)			Notes
30	010709	Male	More than 10 copies	010926	Female 3, Male 1	Female 3	No offspring were obtained after the first delivery. Testes are small and sperm are not observed.
31	010709	Male	2 to 3 copies	010927	Female 3, Male 5	0	Mosaic for gene transfer
				011022	Male 2	0	
				011108	Female 4, Male 6	0	
34	010709	Male	2 to 3 copies	No fertility properties	-	-	Testes are small and sperm are not observed.
46	010821	Male	2 to 3 copies	No fertility properties	-	-	Testes are small and sperm are not observed.

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Please replace the Table 3 on page 29 with the following amended Table 3:

Table 3

Sex	Individual Number	Number of Deliveries	Offspring (Non-Tgm)	Offspring (Tgm)
Female	1	2	Female 3, Male 1	Female 1, Male 6
Female	2	2	Female 4, Male 3	Female 2, Male 1
Female	3	2	Female 2, Male 4	Female 2, Male 2

Please replace the paragraph beginning at page 31, line 5, with the following amended paragraph:

PepT1 expressing budded baculovirus (PepT1-BV) (1 μg/lane) was subjected to SDS-PAGE analysis on 12% gel under reducing conditions. After the electrophoresis, proteins were electroblotted onto a polyvinylidene difluoride (PVDF) membrane. This membrane was reacted

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with 1,000 fold-diluted serum samples, sequentially washed, and then reacted with a 1,000 fold-diluted Biotin-Anti-Mouse IgG(γ) (Zymed) and Streptavidin-Alkaline Phosphatase (Zymed). An alkaline phosphatase staining kit (Nakarai Tesque) was used for staining. A positive control antibody for detecting gp64 was purchased from NOVAGEN.

Please replace the paragraph beginning at page 31, line 21, with the following amended paragraph (note that the only change is to correct the numbering of the example):

[Example [[8]] 9] Production of anti-PepT1 antibodies by gp64 Tgm

Please replace the paragraph beginning at page 32, line 16, with the following amended paragraph:

For example, an exogenous gene expression system, known as the baculovirus expression system, is useful as a tool for obtaining recombinant proteins easily and in large quantities. In particular, when applied to membrane proteins, the baculovirus expression system is excellent in that the membrane proteins are obtainable with other viral envelope proteins in a state that maintains their structure. However, this expression system is also problematic in that, when using this expression product as the immunogen, gp64 acts as a background ~~protein~~ antigen and interferes with the acquisition of antibodies against a target ~~protein~~ antigen.

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Amendments to the Claims:

This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims:

1. (Original) A method for producing an antibody that recognizes a target antigen, wherein the method comprises the steps of:

i) immunizing a non-human animal that has immunotolerance to a background antigen comprised in an immunogen, wherein the immunogen comprises both the target antigen and the background antigen; and

ii) obtaining an antibody against the target antigen, or a gene encoding the antibody.

2. (Original) The method of claim 1, wherein immunotolerance is induced artificially.

3. (Original) The method of claim 1, wherein the non-human animal is a transgenic non-human animal.

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4. (Original) A method for producing an antibody against a target antigen, wherein the method comprises the steps of:

(a) preparing an immunogen comprising the target antigen and a background antigen;

(b) producing a transgenic non-human animal comprising a gene expressibly encoding the background antigen;

(c) administering the immunogen of (a) to the transgenic non-human animal of (b); and

(d) isolating the antibody against the target antigen from the transgenic non-human animal.

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5. (Original) The method of claim 4, wherein the immunogen is a virus particle or a part thereof.

6. (Original) The method of claim 5, wherein the virus is a baculovirus.

7. (Original) The method of claim 4, wherein the target antigen is a membrane protein.

8. (Original) The method of claim 6, wherein the background antigen is gp64.

9. (Original) The method of claim 4, wherein the non-human animal is a mouse.

10. (Currently Amended) An antibody that is produced by the method of ~~any one of claims 1 to 9~~ claim 1.

11. (Original) A chimeric antibody between a non-human animal and human, or a humanized antibody, produced using the antibody of claim 10.

12. (Original) A transgenic non-human animal, into which a gene encoding a viral envelope protein is introduced.

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13. (Original) The transgenic non-human animal of claim 12, wherein the virus is a baculovirus.

14. (Original) The non-human animal of claim 13, wherein the viral envelope protein is gp64.

15. (Original) The non-human animal of claim 12, wherein the non-human animal is a mouse.

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16. (Original) The non-human animal of claim 12, for use in producing an antibody against an antigen comprising a viral protein.

17. (Original) A method for producing a non-human immunized animal, wherein the method comprises the step of producing a transgenic non-human animal into which a gene encoding a background antigen is introduced.

18. (Original) A non-human immunized animal for obtaining an antibody against a target antigen comprising a background antigen, wherein the animal is produced by the method of claim 17.

19. (Original) A method for producing an antibody against PepT1, wherein the method comprises the steps of:

(a) preparing a baculovirus that expressibly comprises a DNA which encodes PepT1 or a fragment thereof;

(b) infecting a host cell with the baculovirus of (a) to obtain a budding virus that expresses PepT1 or a fragment thereof;

(c) producing a transgenic non-human animal that expressibly comprises a gene encoding a baculovirus membrane protein gp64;

(d) immunizing the transgenic non-human animal of (c) with a fraction comprising the budding virus of (b) or PepT1 or its fragment; and

(e) recovering the antibody-recognizing PepT1 from the immunized animal.

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20. (New) An antibody that is produced by the method of claim 4.

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Amendments to the Drawings:

The attached replacement sheet of drawings includes changes to Fig. 1 and replaces the original sheet including Fig. 1.

In Figure 1, the line denoting the EcoR1 restriction enzyme recognition site has been moved from after the "t" to after a "c."

Attachments following last page of this Amendment:

Replacement Sheet (1 page)
Annotated Sheet Showing Change (1 page)

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REMARKS

The amendments to the specification clarify the translated text, correct errors, and, identify abbreviations and trademark information in the original Japanese specification, all of which are apparent when read in the context of the entire specification. The amendments also correct the title and insert into the specification a paper copy of the sequence listing in which the general information has been updated to reflect accurate information for the instant application. In addition Fig. 1 is amended to move the line denoting the EcoR1 restriction enzyme recognition site from after the "t" to after a "c."

Claims 1-20 are pending. Claim 10 is amended to remove multiple dependency. New claim 20 is based on original claim 10. Applicants ask that all claims be examined in view of the amendment to the claims. No new matter has been introduced by these amendments.

Please apply any other charges to deposit account 06-1050, referencing Attorney-Docket No. 14875-137US1.

Respectfully submitted,

Date: December 3, 2004

Janice L. Kugler for
Janis K. Fraser, Ph.D., J.D. 50,429
Reg. No. 34,819

Fish & Richardson P.C.
225 Franklin Street
Boston, MA 02110-2804
Telephone: (617) 542-5070
Facsimile: (617) 542-8906

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